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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,978	02/18/2000	Francois Spertini	18519-001	9105

7590 04/23/2002

Mintz Levin Cohn Ferris Glovsky and Popeo PC
One Financial Center
Boston, MA 02111

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/23/2002 15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,978	SPERTINI, FRANCOIS	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-30, 36-37, 41-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-30, 36-37 and 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 28-30, 36-46 are pending.

2. In view of the amendment filed 1/31/02, only the following objection and rejections remain.

3. The disclosure stands objected to because of Accession No. for hydridoma 5E11 needs to be filled out on page 2 of the specification. It is noted that Applicant will amend the specification upon receipt of an Accession Number.

4. Claims 28-30, 36-37 and 41-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating an immune response, said method comprising administering a substantially pure polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof in an amount sufficient to inhibit an immune reaction by the subject against said polypeptide, the said method further comprising administering a second bee venom polypeptide selected from the group consisting of the ones recited in claim 30, does not reasonably provide enablement for *any* method of modulating an immune response wherein said method comprising administering a substantially pure polypeptide comprising (1) *any* fragment of the amino acid sequence of SEQ ID NO: 1, (2) *any* fragment of between 40 and 66 amino acids in length to a subject in need thereof in an amount sufficient to inhibit an immune reaction by the subject against said polypeptide, (3) the said method further comprising administering any one or more additional bee venom polypeptides to said subject, (4) *any* method of modulating an immune responses, said method comprising administering any one or more substantially pure polypeptides wherein said one or more polypeptides "comprises" *any* "fragments" of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof, in an amount sufficient to inhibit an immune reaction by the subject against said one or more polypeptides to said subject, (5) the said method wherein said one or more additional bee venom polypeptides are selected from the ones recited in claim 46. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 12.

Applicants' arguments filed 1/31/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended to recite the polypeptide comprising SEQ ID NO: 1; (2) claims 37 and 44 have been amended to recite the peptide fragment is between 40 and 66 amino acids in length and no new matter is introduced; (3) claims 38-40 have been cancelled and (4) Applicants submitted that claims 37 and 44 as amended related to Api m6.04, a 73 amino acid peptide (designated SEQ ID NO: 4) and three long fragments of this peptide: Api m 6.01, a 67 amino acid peptide designated as SEQ ID NO: 1, Api m6.02 a 69 amino acid peptide designated as SEQ ID NO: 2 and Api m 6.03, a 71 amino peptide designated as SEQ ID NO: 3.

However, the amended claims 37 and 44 do not recite the specific SEQ ID NOS. Further, the recitation of "**comprising**" is open-ended. It expands the fragments to include additional amino acid residues at either end. There is insufficient guidance and working examples as to the specific amino acid residues that make up the undisclosed peptide fragments and whether any of the undisclosed peptide fragment or fragments would have the same function as SEQ ID NO: 1, in turn, for a method of modulating immune response.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only 4 full-length polypeptides of SEQ ID NOS: 1-4 for a method of inhibiting T cell response in a subject who is sensitive to a protein allergen from bee venom (see page 19).

The specification does not teach how to make and use *any* polypeptide "fragment" of the amino acid sequence of SEQ ID NO: 1 such as between 40-60 amino acid in length and whether *any* of the polypeptide mentioned above have the same structure and/or function such as inhibiting any immune response as SEQ ID NO: 1. There is insufficient guidance and working examples as to the specific amino acid residues that makes up the fragment that is "between 40-

60 amino acids in length" that would have the same function as SEQ ID NO: 1. Further, the term "comprising" is open-ended. It expands the "fragment" to include additional amino acids at either end. Given the indefinite number of undisclosed amino acid in *any* undisclosed fragment, it is unpredictable which undisclosed fragment or fragments would have the same functions and structure as SEQ ID NO: 1 for a method for modulating an immune response wherein the immune response is inhibitory in a subject.

There is insufficient guidance and working examples as to the amino acid positions within the polypeptide of SEQ ID NO: 1 that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function which will require guidance (See Ngo et al., of record, 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function.

Attwood *et al* (of record) teach that "It is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences (and it is not always clear what we mean by "function"); very few structures are known compared with the number of sequences, and structure prediction methods are unreliable (and knowing structure does not inherently tell us functions)".

Fasler *et al.* (of record) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral Asn residue at position 173 either with a basic Lysine, a hydrophobic Try, Ile, an acidic Asp or a hydrophilic residue serine also did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

Burks *et al.* (of record) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in

loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular).

Stanley *et al.* (of record) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley et al also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular).

Skolnick *et al* (of record) teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular).

Colman *et al* (of record) teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular).

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention as broadly as claimed without undue amount of experimentation. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the lack of guidance and the lack of working examples, the breadth of the claims that fail to recite any structural or functional limitations and the unpredictability of the art, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

5. Claims 28-30, 36-37 and 41-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 12.

Applicants' arguments filed 1/31/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) claim 1 has been amended to recite the polypeptide comprising SEQ ID NO: 1; (2) claims 37 and 44 have been amended to recite the peptide

fragment is between 40 and 66 amino acids in length and no new matter is introduced; (3) claims 38-40 have been cancelled and (4) Applicants submitted that claims 37 and 44 as amended related to Api m6.04, a 73 amino acid peptide (designated SEQ ID NO: 4) and three long fragments of this peptide: Api m 6.01, a 67 amino acid peptide designated as SEQ ID NO: 1, Api m6.02 a 69 amino acid peptide designated as SEQ ID NO: 2 and Api m 6.03, a 71 amino peptide designated as SEQ ID NO: 3.

However, the amended claims 37 and 44 do not recite the specific SEQ ID NO. Further, the recitation of "**comprising**" is open-ended. It expands the fragments to include additional amino acid residues at either end.

The specification discloses only 4 full-length polypeptides of SEQ ID NOS: 1-4 for a method of inhibiting T cell response in a subject who is sensitive to a protein allergen from bee venom (see page 19).

The specification does not teach *any* method of modulating an immune response wherein said method comprising administering a substantially pure polypeptide comprising (1) *any* fragment of the amino acid sequence of SEQ ID NO: 1, (2) *any* fragment of between 40 and 66 amino acids in length to a subject in need thereof in an amount sufficient to inhibit an immune reaction by the subject against said polypeptide, (3) the said method further comprising administering any one or more additional bee venom polypeptides to said subject, (4) *any* method of modulating an immune responses, said method comprising administering any one or more substantially pure polypeptides wherein said one or more polypeptides "comprises" any "fragments" of the amino acid sequence of SEQ ID NO: 1 to a subject in need thereof, in an amount sufficient to inhibit an immune reaction by the subject against said one or more polypeptides to said subject, (5) the said method wherein said one or more additional bee venom polypeptides are selected from the ones recited in claim 46.

There is insufficient **written description** about the structure associated with function of *any* fragment of the amino acid sequence of SEQ ID NO: 1, *any* fragment of between 40 and 66 amino acids in length, any one or more additional bee venom polypeptides, one or more polypeptides "comprises" any "fragments" of the amino acid sequence of SEQ ID NO: 1 for a method of modulating an immune response. Further, Applicants disclose only 3 peptide fragments as evidence in the specification and the response filed 1/31/02, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species

to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 28-30, 36-37 and 41-46 are free of prior art.

7. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

9. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
April 22, 2002

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600